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Clinical paper

Cognitive impairment and psychopathology in sudden out-of-hospital cardiac arrest survivors: Results from the REVIVAL cohort study

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Abstract

Aim: To investigate cognitive impairment and psychopathology in out-of-hospital cardiac arrest (OHCA) survivors using a screening procedure during hospitalisation and examine the evolution of these parameters at three-month follow-up.

Methods: This multicentre cohort study screened for cognitive impairment using the Montreal Cognitive Assessment (MoCA), for symptoms of anxiety, depression and traumatic distress using the Hospital Anxiety and Depression Scale (HADS) and the Impact of Event Scale–revised (IES-R) during hospitalisation. At three-month follow-up, we evaluated cognitive impairment with a neuropsychological test battery and symptoms of psychopathology were re-assessed using HADS and IES-R. Logistic regression models were applied to examine associations between screening results and outcomes.

Results: This study included 297 OHCA survivors. During hospitalisation, 65% presented with cognitive impairment, 25% reported symptoms of anxiety, 20% symptoms of depression and 21% symptoms of traumatic distress. At follow-up, 53% reported cognitive impairment, 17% symptoms of anxiety, 15% symptoms of depression and 19% symptoms of traumatic distress. Cognitive impairment during hospitalisation was associated with higher odds (OR (95% CI) 2.55 (1.36–4.75), $p = .02$) of an unfavorable cognitive outcome at follow-up, and symptoms of psychopathology during hospitalisation were associated with higher odds of psychopathology at follow-up across all three symptom groups; anxiety (6.70 (2.40–18.72), $p < .001$), depression (4.69 (1.69–13.02), $p < .001$) and traumatic distress (7.07 (2.67–18.73), $p < .001$).

Conclusion: OHCA survivors exhibited both cognitive impairment and symptoms of psychopathology during hospitalisation comparable to previous studies, which were associated with unfavorable mental health outcomes at three-month follow-up.

Keywords: Resuscitation, Montreal Cognitive Assessment, Mild cognitive impairment, Psychopathology, Screening tool

Introduction

While sudden out-of-hospital cardiac arrest (OHCA) remains a leading cause of death worldwide,[1] survival rates are higher than ever due to successful improvements in pre-hospital and acute medical care regimes.[2,3] In Europe and the United States, the survival rates at hospital discharge are 8% and 11%, respectively.[4] In many cases, mental health complications are a pervasive secondary consequence of resuscitation,[5–8] and cognitive impairment and symptoms of psychopathology are common.[5,8,9] Roughly 50% of cardiac arrest survivors report long-term cognitive impairment,[9] and prolonged psychopathological symptoms of anxiety (15%–24%), depression (13%–15%) and post-traumatic stress disorder (PTSD) (16%–28%) are prevalent.[7,8] These mental health challenges are particularly found in cardiac arrest patients who are admitted in a comatose

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state,[5] which impedes the survivor's recovery,[10,11] interferes with health-related quality of life[12–14] and predicates lower participation in society.[15]

The European Resuscitation Council (ERC) and the European Society for Intensive Care Medicine (ESICM) post-resuscitation guidelines recommend systematic functional assessments prior to hospital discharge;[16] however, screening for cognitive and psychological problems is still not performed routinely. Furthermore, an appropriate screening tool for assessing cognitive impairment and symptoms of psychopathology has not yet been developed for OHCA survivors, and these mental health challenges often go unrecognised.[17] Within 3 month after hospital discharge, the ERC and ESICM advocate evaluating cognitive impairment with the performance-based Montreal Cognitive Assessment (MoCA) tool, and symptoms of anxiety and depression using the self-reported Hospital Anxiety and Depression Scale.[16] The self-reported Impact of Event Scale (IES) has also been suggested for measuring traumatic distress, including PTSD.[17] More insights are needed regarding the usefulness of early in-hospital screening tools for OHCA survivors.

To fill this knowledge gap, we hypothesised that (i) cognitive impairment during hospitalisation is associated with a cognitive unfavorable outcome at three-month follow-up and (ii) symptoms of psychopathology during hospitalisation are associated with risk of psychopathology at three-month follow-up.

Methods

Study design and recruitment procedures

The multicentre REcovery after cardiac arrest surVIVAL (REVIVAL) cohort study (n = 297 patients) was conducted at three highly specialised heart centres in Denmark between January 2018 and February 2022. The cardiac arrest centres in Denmark practice common international protocols for the treatment and care of resuscitated patients, including interventional cardiology, bundled critical care with targeted temperature management, protocolised cardiorespiratory support and prognostication.[16] The protocol for this study was previously published.[18]

Inclusion and exclusion criteria

Inclusion criteria targeted unconscious or conscious first-time OHCA survivors with sustained return of spontaneous circulation (ROSC) and with a suspected cardiac aetiology for cardiac arrest as defined by the Utstein template.[19] Exclusion criteria included patients with a history of cerebrovascular or traumatic brain injury and those suffering from a serious untreatable somatic or psychiatric disease or lacking Danish language abilities to complete the screening procedure.

Recruitment

Comatose patients were approached preferably on day four ($\geq$72 hours) after sedatives were terminated. Patients admitted awake were clinically stable. All patients provided informed written consent after consulting with a close relative.

Ethics

The REVIVAL study complies with the ethical principles of the Declaration of Helsinki.[20] The Danish Data Protection Agency approved the handling of data (RH-2017-325), I-Suite (05961), and the regional Research Ethic Committee (H-18046155) approved the study before the inclusion of survivors.

Data collection and measures

Data collected during hospitalisation (T1)

Data collected during hospitalisation (T1 data) included socio-demographics, medical pre-arrest history, clinical characteristics related to cardiac arrest, MoCA, HADS and IES-R. Screenings were conducted by a certified cardiac project nurse at Copenhagen University Hospital, Rigshospitalet, University Hospital Herlev-Gentofte and Odense University Hospital. For those admitted awake after a brief time to ROSC, the median time for T1 data collection was four days (interquartile range (IQR): 1–5). For the patients admitted comatose, the median data collection time was six days (IQR: 5–8) after termination of sedatives. The most common reason for earlier assessment (<four days) of comatose patients was impending transfer to another hospital, whereas the most common reasons for delayed assessment (>nine days) were psychological distress and mental exhaustion.

Data collected at three-month follow-up (T2)

Data collected at three-month follow-up (T2 data) included a neuropsychological test battery and repeated HADS and IES-R which were sent to participants via email and completed online. Trained psychology students or a cardiac nurse administered the neuropsychological test battery following a predefined written study manual. The assessments took place in undisturbed test-facilities at the hospital. Due to the COVID-19 pandemic, we allowed neuropsychological testing to take place in the homes of some of the survivors (n = 21). Six survivors had delayed follow-up assessments. The overall median time from T1 to T2 data collection was three months (IQR: 3–3.5).

Measures

Socio-demographic and clinical characteristics

At T1, we collected self-reported socio-demographic variables of age, sex, ethnicity, cohabitation, and level of education prior to cardiac arrest. The International Standard Classification of Education (ISCED)[21] was used for education levels, which were divided into three groups (Table 1). Clinical characteristics of the cardiac arrest were retrieved from pre-hospital records and medical charts.

Montreal cognitive assessment

At T1, we screened the cognitive status of survivors using the Danish 7.0 version of the brief paper and pencil MoCA.[22] The MoCA is the preferred screening instrument for assessing post-arrest cognitive impairment.[4] MoCA takes approximately 10 minutes and associated tasks cover the general domains of cognition: visuospatial abilities and executive functioning, memory, attention, language and orientation, including 30 items (each scored with 1 point) where a higher score reflects better performance. One point was also added for education level <12 years. We applied the suggested threshold <26 to indicate cognitive impairment.[22,23]

The neuropsychological test battery

At T2, all participants underwent an extensive neuropsychological test battery to assess performance in the three main cognitive domains of episodic memory, visuospatial abilities and executive function (Supplementary Material Table S1). The test battery includes the Verbal Affective Memory Task–26,[24] Rey's Complex Figure[25] and Delis–Kaplan Executive System tests,[26] including Trail making, Verbal fluency, Design fluency and Colour-word-

Table 1 – Baseline patient and cardiac arrest characteristics.

Patient characteristics	Total population n = 297
Age, mean (SD), years	58.2 (12.7)
Median (IQR), years	59 (50–67)
Male sex %	84
Married/living with partner %	82
Level of education	
ISCED levels 0–2%	20
ISCED levels 3 and 5%	60
ISCED levels 6–8%	20
Characteristics related to cardiac arrest	
Place of OHCA	
Home %	43
Public space %	54
Other (e.g. ambulance) %	<5
Cause of cardiac arrest	
Ischaemic heart disease %	68
Other (cardiomyopathies, ion channel diseases, idiopathic ventricular fibrillation) %	32
Bystander witnessed cardiac arrest %	91
Bystander performed CPR %	95
Initial shockable cardiac rhythm %	98
Time to ROSC, median (IQR), minutes	10 (7–16)
Treated at the ICU %	63
Mechanical ventilated %	61
Induced hypothermia %	50
Length of hospital admission, median (IQR), days	12 (8–17)

ISCED: International Standard Classification of Education (21): Level 0–2: pre-primary, primary and lower secondary education, level 3 and 5: upper secondary education (high school) or vocational training and short-cycle tertiary education (there is no education corresponding to level 4 I Denmark), level 6–8: median length tertiary education, bachelor, master and PhD degrees. **OHCA:** out-of-hospital cardiac arrest, **CPR:** cardiopulmonary resuscitation, **ROSC:** return of spontaneous circulation, **ICU:** intensive care unit.

interference tests. We also administered the letter-number sequencing test from the Wechsler Adult Intelligence Scale-IV.[27] As our primary cognitive outcome, test performance was dichotomised into whether the patients exhibited a favorable outcome or an unfavorable outcome, the latter defined as 1.5 SD on 1 test or 1 SD on ≥2 tests below the norm population mean or reference data mean. The data were stratified according to age and means were calculated for each age group.

Psychopathological screening

At T1 and T2, we evaluated symptoms of anxiety, depression and traumatic distress using the Danish patient-reported outcome versions of the 14-item HADS and the 22-item IES-R. The HADS scale[28] includes two subscales (HADS-A for anxiety and HADS-D for depression) with seven items for each subscale. Items are rated on a four-point Likert scale ranging from 0 ('no symptoms') to 3 ('extreme symptoms'). IES-R items are rated on a five-point Likert scale ranging from 0 ('not at all') to 4 ('extremely'). We employed a cut-off score of ≥8 on HADS for the likely presence of anxiety and/or depression[29] and a cut-off score of ≥30 on IES-R for a likely presence of traumatic distress.[30]

Data analyses

We present summary statistics of socio-demographics, and clinical data related to the cardiac arrest as proportions in percentage (%) for categorical variables, means with standard deviations (M ± SD) for continuous approximately normally distributed data and medians with IQR for non-normally distributed data. The Wilcoxon rank-sum test was used to compare age distributions between males and females. The descriptive distribution of MoCA subscale scores is illustrated with box-and-whisker plots.

We compared socio-demographic data, and clinical characteristics of non-responders of HADS and IES-R during hospitalisation and dropouts at the follow-up to the participants using Pearsons X^2 and Fishers Exact tests. MoCA, HADS and IES-R scores during hospitalisation for survivors with whom we lost contact to were compared with follow-up participants using Wilcoxon rank-sum tests. Differences in cognitive and psychopathological measures during hospitalisation between patients admitted unconscious and conscious and at three months were compared using students' *t*-tests and chi-squared tests.

We used chi-squared tests and Wilcoxon rank-sum tests to compare distributions of sex, age and time to ROSC across groups at T1 and T2 (MoCA < 26 vs. MoCA ≥ 26/neuropsychological favorable outcome vs. unfavorable outcome, HADS ≥ 8 vs. HADS < 8 and IES-R ≥ 30 vs. IES-R < 30). Neuropsychological data at follow-up were transformed into z-scores, using means and standard deviations from norm or reference data. The survivors were divided into favorable outcome and unfavorable outcome groups. Four logistic regression models were used to examine associations between MoCA, HADS-A, HADS-D and IES-R during hospitalisation and follow-up outcome measures of neuropsychological status (favorable outcome and unfavorable outcome), HADS-A, HADS-D and IES-R. Age, sex, time to ROSC and conscious state at admission were included as covariates in all regression models. Estimates are presented as adjusted odds ratios (ORs) and corresponding 95% confidence intervals (CIs). Data were analysed using STATA 15.1 (StataCorp, 2017; Stata Statistical Software: Release 15, Stata Corp LLC, College Station, Texas, USA). Data descriptions are reported according to STROBE guidelines for observational study reporting.[31] An alpha level of 0.05 was considered the threshold for statistical significance.

Results

T1 participant characteristics

Socio-demographic, and clinical characteristics

A total of 665 OHCA survivors were admitted and treated at the participating cardiac arrest centres (Fig. 1). Due to exclusions and deaths, 297 OHCA survivors (16% women) were enrolled. Of these, 188 patients (63%) were hospitalised unconscious. Table 1 presents baseline socio-demographic, and clinical characteristics. The ethnic majority group (98%) was Caucasian with Danish descent. The remaining 2% were of Asian or Middle Eastern descent, but all with good Danish proficiency. Participants' median age was 59 years (IQR 50–67). Female survivors were younger than male survivors (54 vs. 60 years, p = .001).

MoCA scores during hospitalisation

Fig. 1 shows that all 297 survivors were screened with MoCA. The MoCA median score was 24 (IQR: 21–26), with 65% exhibiting

cognitive impairment (<26). Impaired memory, followed by problems with visuospatial abilities and executive function predominated (Supplementary Material Fig. S1)). We only observed minor deficits in attention tasks. Patients admitted comatose exhibited a MoCA score <26 more often compared with those admitted awake (72% vs. 52%, $p = .001$) (Table 2). Survivors with a MoCA score <26 were older than the MoCA ≥ 26 group (60 years vs. 57 years $p = .001$). We found no significant differences in the distribution of sex and time to ROSC between the MoCA groups.

HADS and IES-R scores during hospitalisation

As presented in Fig. 1, 269 survivors completed the HADS and 264 completed the IES-R. The median HADS-A score was 5 (IQR: 2–8), and 25% reported symptoms of anxiety (HADS-A score ≥ 8).

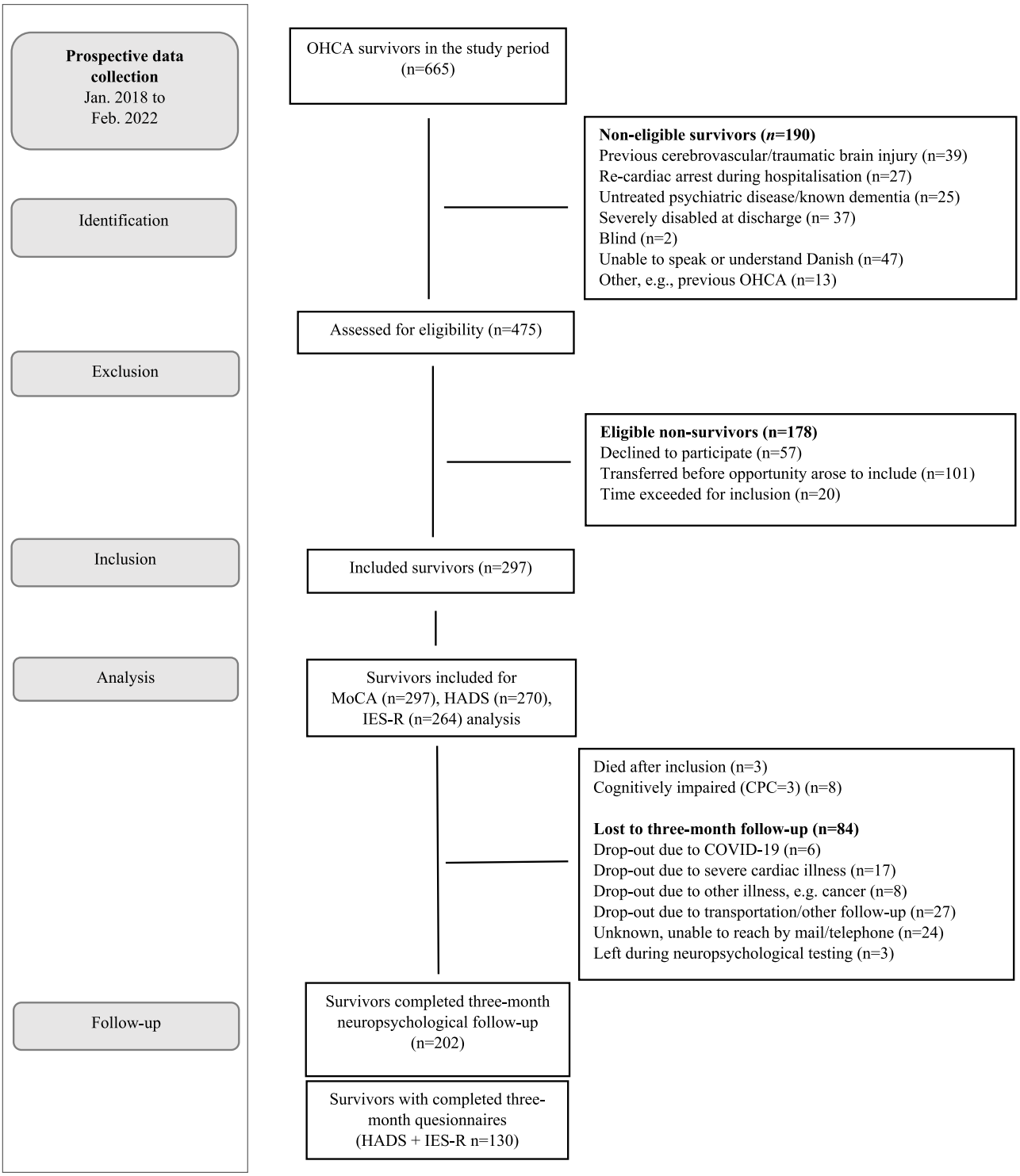

Fig. 1 – The REVIVAL flow chart in line with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement (http://www.strobestatement.org).

The median HADS-D score was 3 (IQR: 1–7), and 20% reported symptoms of depression (HADS-D score ≥8). The median IES-R score was 17 (IQR: 8–27), with 21% reporting symptoms of traumatic distress as indicated by an IES-R score ≥30. Table 2 shows that patients admitted comatose reported HADS-A ≥8 more often (29% vs. 18%, $p = .02$). Survivors with an IES-R score ≥ 30 were younger compared with those with an IES-R < 30 (58 years vs. 60 years $p = .04$) and had a longer time to ROSC (15 minutes vs. 10 minutes, $p = .005$). We found no differences in the distribution of sex.

Non-responders of HADS and IES-R

The small group of non-responders during hospitalisation (T1 HADS: $n = 28$ and IES-R: n = 33) did not differ from participants according to socio-demographic, and clinical characteristics.

T2 outcomes

T2 participants characteristics at follow-up

At T2, 294 of the previous T1 population were alive. Of these, 28% were unreachable for follow-up, leaving 202 participants in neuropsychological testing. These respondents had higher education levels (ISCED 3–8) (84% vs. 80%, $p = .01$), and less exhibited a MoCA score < 26 (median 25 vs. 24, $p < .001$) compared with the overall population.

Unfavorable cognitive outcome at follow-up

As shown in Table 2, 107 patients (53%) exhibited a cognitive unfavorable outcome. All cognitive domains were affected. Patients admitted comatose at T1 presented a cognitive unfavorable outcome more often (54% vs. 52%, $p = .04$) compared with those admitted awake. We found no differences in the distribution of age, sex and time to ROSC.

Clinical levels of psychopathology at follow-up

A total of 129 survivors completed HADS and IES-R at T2 (Table 2), with a median HADS-A score of 3 (IQR: 1–5) and 17% reporting clinical levels of anxiety. The median HADS-D score was 2 (IQR: 0–5), with 15% reporting clinical levels of depression. The median IES-R was 10 (IQR: 6–21), with 19% reporting clinical levels of PTSD. Survivors with HADS-A ≥ 8 and IES-R ≥ 30 scores were more often females than males compared with survivors with HADS-A < 8 (46% vs. 10%, $p < .001$) and IES-R < 30 (54% vs. 9%, $p < .001$) scores. We found no significance between group differences in age or time to ROSC.

Associations between MoCA during hospitalisation and cognitive outcome at follow-up

The adjusted logistic regression model revealed statistically significant higher odds of exhibiting an unfavorable cognitive outcome at T2 with a MoCA score <26 at T1 (OR 2.55; 95% CI, 1.36–4.75, $p = .02$). We found no effect of sex, age, time to ROSC and conscious state at admission.

Association between HADS and IES-R during hospitalisation and at follow-up

Symptoms of anxiety at T1 were associated with statistically significant higher odds of clinical levels of anxiety at T2 (OR 6.70; 95% CI, 2.40–18.72, $p < .001$) and symptoms of depression at T1 were associated with clinical levels of depression at T2 (OR 4.69; 95%

Table 2 – Differences between patients admitted unconscious and conscious on cognitive and psychopathological measures during hospitalisation (T1) and at three-month follow-up (T2).

	Total population		Unconscious at admission		Conscious at admission		P[a]	P[b]
	T1 $n = 297$	T2 $n = 202$	T1 $n = 188$	T2 $n = 127$	T1 $n = 109$	T2 $n = 75$		
Cognition								
MoCA								
Total MoCA mean ± SD	23.3 ± 4.2	N/A	22.6 ± 4.3	N/A	24.5 ± 3.7	N/A	0.0001*	
Median (IQR)	24 (21–26)		24 (20–26)		25 (23–27)			
MoCA < 26, *n* (%)	192 (65)	N/A	135 (72)	N/A	57 (52)	N/A	0.001*	
Neuropsychological test								
Unfavourable cognitive outcome	N/A	107 (53)	N/A	68 (54)	N/A	39 (52)		0.04*
Psychopathology								
HADS	$n = 269$	$n = 129$	$n = 170$	$n = 78$	$n = 99$	$n = 51$		
HADS-A mean (SD)	5.7 (3.9)	3.8 (4.0)	5.9 (3.8)	3.9 (4.0)	5.2 (3.9)	3.7 (4.0)	0.16	0.69
Median (IQR)	5 (2–8)	3 (1–5)	5 (3–9)	3 (1–5)	5 (2–7)	3 (1–4)		
HADS-A ≥ 8, *n* (%)	68 (25)	22 (17)	50 (29)	15 (19)	18 (18)	7 (14)	0.02*	0.42
HADS-D mean (SD)	4.6 (3.7)	3.2 (3.8)	4.9 (3.7)	3.0 (3.8)	4.0 (3.6)	3.5 (3.7)	0.11	0.62
Median (IQR)	3 (1–7)	2 (0–5)	4 (2–7)	2 (0–5)	3 (1–6.5)	2 (1–6)		
HADS-D ≥ 8, *n* (%)	53 (20)	19 (15)	37 (22)	11 (14)	16 (16)	8 (16)	0.22	0.95
IES-R	$n = 264$	$n = 129$	$n = 165$	$n = 78$	$n = 98$	$n = 51$		
IES-R mean (SD)	19.5 (13.7)	15.6 (15.0)	20.5 (14.7)	15.4 (15.0)	17.8 (12.0)	16.0 (15.2)	0.13	0.79
Median (IQR)	17 (8–27)	10 (6–21)	18.5 (9–30)	10.5 (5–21)	16 (7.5–26)	10 (6–22)		
IES-R ≥ 30, *n* (%)	55 (21)	25 (19)	38 (25)	14 (18)	17 (18)	11 (22)	0.08	0.96

T1: During hospitalisation, T2: At follow-up, MoCA: Montreal Cognitive Assessment, HADS-A: Hospital Anxiety and Depression Scale – Anxiety, HADS-D: Hospital Anxiety and Depression Scale – Depression, IES-R: Impact of Event Scale-Revised.

[a] Test of T1 difference between the unconscious admitted group and the conscious admitted group. Student's *t*-test for continuous variables and Chi-square test for categorical variables.

[b] Test of T2 differences between the unconscious admitted group and the conscious admitted group. Student's *t*-test for continuous variables and Chi-square test for categorical variables.

CI, 1.69–13.02, $p < .001$). Using IES-R as an early screener, we also found a strong significant association between traumatic distress at T1 and higher odds of clinical levels of PTSD at T2 (OR 7.07; 95% CI, 2.67–18.73, $p < .001$). Females were more strongly associated with anxiety at T2 (HADS-A $\geq$ 8) and PTSD (IES $\geq$ 30), $p < .001$). We found no effect of age, time to ROSC and conscious state at admission.

Discussion

This large cohort study extends previous research on cognitive impairment and psychopathology in OHCA survivors, demonstrating associations between an early screening during hospitalisation and mental health outcomes at three month follow-up emphasising the importance of early routine mental health screening.

Using a MoCA threshold <26 indicating cognitive impairment, 65% of survivors exhibited difficulties with memory, visuospatial abilities and executive function which aligns with previous research.[5,9] Comparable to existing resuscitation studies (three to six months post-arrest),[32–34] we also found approximately 50% of survivors to be cognitively impaired at three months. In small studies, the MoCA has been established as a useful early stand-alone screening-tool for cognitive impairment after resuscitation.[35,36] Our research adds to the existing evidence, as we determined that cognitive impairment during hospitalisation is associated with higher odds of cognitive unfavorable outcome at three months in a cohort of solely OHCA survivors. This finding mirrors previous results in stroke patients[37] indicating that MoCA screening predicted subsequent long-term cognitive impairment. As expected, the patients admitted unconscious were found with cognitive impairment more often compared with those admitted awake (T1: 72% vs. 52% and T2: 54% vs. 52%). These findings are congruent with the multidimensional concept of post-intensive care syndrome, which is characterised by neuropsychiatric disabilities following critical illness.[38] We suggest that healthcare providers in clinical practice can identify possible cognitive impairment and provide OHCA survivors with appropriate information, support and rehabilitation plans through routine early use of the MoCA.

Using HADS with a threshold of $\geq$8 indicating symptoms of anxiety and depression, and IES-R with a threshold of $\geq$30 indicating traumatic distress during hospitalisation, we found that 25% of survivors exhibited symptoms of anxiety, 20% symptoms of depression, and 21% symptoms of traumatic distress. This high in-hospital prevalence of symptoms of psychopathology aligns with previous research,[39] particularly a recent systematic review and meta-analysis performed by Yaow et al.[40] Furthermore, at three months, the most common clinical psychopathological symptoms included traumatic distress (19%) and anxiety (17%), in accordance with current resuscitation literature[7,41,42] when considering post-arrest psychological symptoms at three to six months follow-up. Notably, we found that symptoms of psychopathology during hospitalisation were associated with higher odds of clinical levels of psychopathology at follow-up across all three symptom groups, introducing critical research insights. The HADS and the IES-R tools could be used to identify patients at risk of developing psychopathology prior hospital discharge, enabling targeted prevention.

As determined in other resuscitation studies addressing anxiety, depression and/ or traumatic reactions,[7,39,43,44] we found higher distribution of women and younger survivors with elevated levels of psychopathology symptoms. This has urgent clinical implications, stressing the importance of an early targeted management approach for the most vulnerable survivors at risk of psychological sequelae.

Limitations

The main limitation of our study design is its observational nature, which precludes examinations of causal relationships. We applied strict exclusion criteria to investigate the effect of cardiac arrest on cognitive impairment and clinical levels of psychopathology which may have biased the representativeness of the study population. Moreover, it seems urgent to establish a normative cut-off score for traumatic distress and PTSD in resuscitation research. As expected, the most critically ill survivors were lost to follow-up. The fact that we were unable to collect cognitive and psychopathological data from these survivors may have challenged the internal validity of the study and influenced our conclusions, underestimating the post-arrest prevalence of cognitive impairment and clinical levels of psychopathology. Furthermore, as females represent a minority, making up only 16% of our sample size, the sex-specific results must be interpreted with caution.

Conclusions

The results of this multicentre prospective cohort study emphasise the importance of routine early mental health screening of OHCA survivors during hospitalisation. Based on our results, we suggest MoCA, HADS and IES-R as useful screening tools in future cardiac arrest research and clinical practice for identifying cognitive impairment and psychopathology.

CRediT authorship contribution statement

Mette Kirstine Wagner: Writing – review & editing, Writing – original draft, Project administration, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Selina Kikkenborg Berg:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Christian Hassager:** Writing – review & editing, Supervision, Formal analysis, Conceptualization. **Britt Borregaard:** Writing – review & editing. **Trine Bernholdt Rasmussen:** Writing – review & editing. **Ola Ekholm:** Writing – review & editing, Software, Methodology, Formal analysis. **Dea Siggaard Stenbæk:** Writing – review & editing, Supervision, Resources, Methodology, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

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REFERENCES

1. Kiguchi T, Okubo M, Nishiyama C, et al. Out-of-hospital cardiac arrest across the World: First report from the International Liaison Committee on Resuscitation (ILCOR). Resuscitation 2020;152:39–49. https://doi.org/10.1016/j.resuscitation.2020.02.044.
2. Daya MR, Schmicker RH, Zive DM, et al. Out-of-hospital cardiac arrest survival improving over time: Results from the Resuscitation Outcomes Consortium (ROC). Resuscitation 2015;91:108–15. https://doi.org/10.1016/j.resuscitation.2015.02.003.
3. Mozaffarian D, Benjamin EJ, Go AS, et al. Executive summary: heart disease and stroke statistics-2016 update: a report from the American heart association. Circulation 2016;133:447–54. https://doi.org/10.1161/cir.0000000000000366.
4. Gräsner JT, Herlitz J, Tjelmeland IBM, et al. European Resuscitation Council Guidelines 2021: Epidemiology of cardiac arrest in Europe. Resuscitation 2021;161:61–79. https://doi.org/10.1016/j.resuscitation.2021.02.007.
5. Zook N, Voss S, Blennow Nordstrom E, et al. Neurocognitive function following out-of-hospital cardiac arrest: A systematic review. Resuscitation 2022;170:238–46. https://doi.org/10.1016/j.resuscitation.2021.10.005 [published Online First: 2021/10/15].
6. Cronberg T, Greer DM, Lilja G, et al. Brain injury after cardiac arrest: From prognostication of comatose patients to rehabilitation. Lancet Neurology 2020;19:611–22. https://doi.org/10.1016/s1474-4422(20)30117-4.
7. Lilja G, Nilsson G, Nielsen N, et al. Anxiety and depression among out-of-hospital cardiac arrest survivors. Resuscitation 2015;97:68–75. https://doi.org/10.1016/j.resuscitation.2015.09.389 [published Online First: 2015/10/04].
8. Wilder Schaaf KP, Artman LK, Peberdy MA, et al. Anxiety, depression, and PTSD following cardiac arrest: A systematic review of the literature. Resuscitation 2013;84:873–7. https://doi.org/10.1016/j.resuscitation.2012.11.021.
9. Moulaert VRMP, Verbunt JA, van Heugten CM, et al. Cognitive impairments in survivors of out-of-hospital cardiac arrest: A systematic review. Resuscitation 2009;80:297–305. https://doi.org/10.1016/j.resuscitation.2008.10.034.
10. Blennow Nordström E, Lilja G. Assessment of neurocognitive function after cardiac arrest. Current Opinion in Critical Care 2019;25:234–9. https://doi.org/10.1097/mcc.0000000000000607.
11. Haywood K, Whitehead L, Nadkarni VM, et al. COSCA (Core Outcome Set for Cardiac Arrest) in adults: An advisory statement from the international liaison committee on resuscitation. Resuscitation 2018;127. https://doi.org/10.1016/j.resuscitation.2018.03.022.
12. Haywood KL, Pearson N, Morrison LJ, et al. Assessing health-related quality of life (HRQoL) in survivors of out-of-hospital cardiac arrest: A systematic review of patient-reported outcome measures. Resuscitation 2018;123:22–37. https://doi.org/10.1016/j.resuscitation.2017.11.065.
13. Whitehead L, Perkins GD, Clarey A, et al. A systematic review of the outcomes reported in cardiac arrest clinical trials: THE need for a core outcome set. Resuscitation 2015;88:150–7. https://doi.org/10.1016/j.resuscitation.2014.11.013.
14. Elliott VJ, Rodgers DL, Brett SJ. Systematic review of quality of life and other patient-centred outcomes after cardiac arrest survival. Resuscitation 2011;2016:247–56. https://doi.org/10.1016/j.resuscitation.2010.10.030.
15. Lilja G, Nielsen N, Bro-Jeppesen J, et al. Return to work and participation in society after out-of-hospital cardiac arrest. Circulat Cardiovasc Qual Outcomes 2018:11. https://doi.org/10.1161/CIRCOUTCOMES.117.003566.
16. Nolan JP, Sandroni C, Bottiger BW, et al. European Resuscitation Council and European Society of Intensive Care Medicine Guidelines 2021: Post-resuscitation care. Resuscitation 2021;161:220–69. https://doi.org/10.1016/j.resuscitation.2021.02.012 [published Online First: 2021/03/29].
17. Nolan JP, Soar J, Cariou A, et al. European Resuscitation Council and European Society of Intensive Care Medicine Guidelines for Post-resuscitation Care 2015: Section 5 of the European Resuscitation Council Guidelines for Resuscitation 2015. Resuscitation 2015;95:202–22. https://doi.org/10.1016/j.resuscitation.2015.07.018.
18. Wagner MK, Berg SK, Hassager C, et al. Cognitive impairment and psychopathology in out-of-hospital cardiac arrest survivors in Denmark: The REVIVAL cohort study protocol. BMJ Open 2020;10:1–9. https://doi.org/10.1136/bmjopen-2020-038633.
19. Perkins GD, Jacobs IG, Nadkarni VM, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: Update of the Utstein resuscitation registry templates for out-of-hospital cardiac arrest a statement for healthcare professionals from a task force of the international liaison committee. Resuscitation 2015;2016:328–40. https://doi.org/10.1016/j.resuscitation.2014.11.002.

20. World Medical Association Declaration of Helsinki. ethical principles for medical research involving human subjects. J Am College Dent 2014;81:14–8.
21. UNESCO. https://ec.europa.eu/eurostat/statistics-explained/index.php?title=International_Standard_Classification_of_Education_(ISCED).
22. Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal cognitive assessment, MoCA: A brief screening. J Am Geriatr Soc 2005:695–9. https://doi.org/10.1111/j.1532-5415.2005.53221.x.
23. van Gils P, van Heugten C, Hofmeijer J, et al. The Montreal Cognitive Assessment is a valid cognitive screening tool for cardiac arrest survivors. Resuscitation 2021;2022:130–6. https://doi.org/10.1016/j.resuscitation.2021.12.024.
24. Jensen CG, Hjordt LV, Stenbæk DS, et al. Development and psychometric validation of the verbal affective memory test. Memory 2016;24:1208–23. https://doi.org/10.1080/09658211.2015.1087573.
25. Meyers JE, Meyers KR. Rey complex figure test and recognition trial: professional manual. Odessa: Psychological Assessment Resources; 1995.
26. Delis DC, Kaplan E, Kramer JH. Examiner's manual for the Delis-Kaplan executive function system. Child Neuropsychology 2001.
27. Wechsler D, Coalson DL, Raiford SE. WAIS-IV technical and interpretive manual. San Antonio (Texas): Pearson; 2008.
28. Snaith RP. The hospital anxiety and depression scale. Health Qual Life Outcomes 2003;1:29. https://doi.org/10.1186/1477-7525-1-29.
29. Christensen AV, Dixon JK, Juel K, et al. Psychometric properties of the Danish Hospital Anxiety and Depression Scale in patients with cardiac disease: Results from the DenHeart survey. Health Qual Life Outcomes 2020;18:1–13. https://doi.org/10.1186/s12955-019-1264-0.
30. Wagner MK, Nielsen L, Berg SK, et al. Clinical utility of the Danish version of the IES-R in identifying Acute Stress Disorder in sudden Out-of-Hospital Cardiac Arrest Survivors: Results from the multicenter REVIVAL cohort study. Unpubl Work. 2023.
31. Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): Explanation and elaboration. PLoS Med 2007;4:1628–54. https://doi.org/10.1371/journal.pmed.0040297.
32. Ørbo M, Aslaksen PM, Larsby K, et al. Determinants of cognitive outcome in survivors of out-of-hospital cardiac arrest. Resuscitation 2014;85:1462–8. https://doi.org/10.1016/j.resuscitation.2014.08.010.
33. Lilja G, Nielsen N, Friberg H, et al. Cognitive function in survivors of out-of hospital cardiac arrest after target temperature management at 33 degrees C versus 36 degrees C. Circulation 2015;131:1340–9. https://doi.org/10.1161/circulationaha.114.014414.
34. Steinbusch CVM, van Heugten CM, Rasquina SMC, et al. Cognitive impairments and subjective cognitive complaints after survival of cardiac arrest: A prospective longitudinal cohort study. Resuscitation 2017;120:132–7. https://doi.org/10.1016/j.resuscitation.2017.08.007.
35. Koller AC, Rittenberger JC, Repine MJ, et al. Comparison of three cognitive exams in cardiac arrest survivors. Resuscitation 2017;116:98–104. https://doi.org/10.1016/j.resuscitation.2017.04.011.
36. Mion M, Magee N, Davis J, et al. Exploring cognitive impairment in the early stages of an out-of-hospital cardiac arrest–a consecutive case series study. Neuropsychol Rehabilit 2022:1–18. https://doi.org/10.1080/09602011.2022.2052325.
37. Zietemann V, Georgakis MK, Dondaine T, et al. Early MoCA predicts long-term cognitive and functional outcome and mortality after stroke. Neurology 2018;91:E1838–50. https://doi.org/10.1212/wnl.0000000000006506.
38. Needham DM, Davidson J, Cohen H, et al. Improving long-term outcomes after discharge from intensive care unit: Report from a stakeholders' conference. Crit Care Med 2012;40:502–9. https://doi.org/10.1097/ccm.0b013e318232da75.
39. Wagner MK, Christensen AV, Hassager C, et al. Sex differences in patient-reported outcomes in the immediate recovery period after resuscitation: Findings from the cross-sectional DenHeart survey. J Cardiovasc Nurs 2022:1–9. https://doi.org/10.1097/jcn.0000000000000914.
40. Yaow CYL, Teoh SE, Lim WS, et al. Prevalence of anxiety, depression, and post-traumatic stress disorder after cardiac arrest: A systematic review and metaanalysis. Resuscitation 2021;2022:82–91. https://doi.org/10.1016/j.resuscitation.2021.11.023.
41. Moulaert VRM, van Heugten CM, Gorgels TPM, et al. Long-term outcome after survival of a cardiac arrest: a prospective longitudinal cohort study. Neurorehabilit Neural Repair 2017;31:530. https://doi.org/10.1177/1545968317697032.
42. Viktorisson A, Sunnerhagen KS, Johansson D, et al. One-year longitudinal study of psychological distress and self- assessed health in survivors of out-of-hospital cardiac arrest. BMJ Open 2019;9:e029756.
43. Armand S, Wagner MK, Ozenne B, et al. The acute traumatic stress response is associated with long-term post-traumatic stress in cardiac arrest survivors and their close relatives. J Cardiovasc Nurs 2021. https://doi.org/10.1097/jcn.0000000000000829.
44. Desai R, Singh S, Patel K, et al. The prevalence of psychiatric disorders in sudden cardiac arrest survivors: A 5-year nationwide inpatient analysis. Resuscitation 2019;136:131–5. https://doi.org/10.1016/j.resuscitation.2019.01.035.